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Does herpes zoster predispose to giant cell arteritis: a geo-epidemiologic study

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Purpose: Giant cell arteritis (GCA) is the most common systemic vasculitis in the elderly and can cause irreversible blindness and aortitis. Varicella zoster (VZ), which is potentially preventable by vaccination, has been proposed as a possible immune trigger for GCA, but this is controversial. The incidence of GCA varies widely by country. If VZ virus contributes to the immunopathogenesis of GCA we hypothesized that nations with increased incidence of GCA would also have increased incidence of herpes zoster (HZ). We conducted an ecologic analysis to determine the relationship between the incidence of HZ and GCA in different countries.

Methods: A literature search for the incidence rates (IRs) of GCA and HZ from different countries was conducted. Correlation and linear regression was performed comparing the disease IR of each country for subjects 50 years of age or older.

Results: We found the IR for GCA and HZ from 14 countries. Comparing the IRs for GCA and HZ in 50-year-olds, the Pearson product-moment correlation (r) was -0.51 , with linear regression coefficient (β) -2.92 (95% CI $-5.41, -0.43$; $p=0.025$) using robust standard errors. Comparing the IRs for GCA and HZ in 70-year-olds, r was -0.40 , with β -1.78 , which was not statistically significant (95% CI $-4.10, 0.53$; $p=0.12$).

Conclusion: Although this geo-epidemiologic study has potential for aggregation and selection biases, there was no positive biologic gradient between the incidence of clinically evident HZ and GCA.

Keywords: epidemiology, shingles, temporal arteritis, immunopathogenesis

Introduction

Giant cell arteritis (GCA) is the most common systemic vasculitis in the elderly and can cause irreversible blindness, myocardial infarction, aortic aneurysm, stroke and rarely death.¹ The incidence of GCA is projected to increase as our population ages, with predicted cost of \$76 billion in the United States alone, by the year 2050.²

Gilden et al and Nagel et al found varicella zoster virus (VZV) in the temporal arteries of 73% of patients with biopsy-proven GCA and propose VZV as a possible trigger in the immunopathogenesis of GCA.^{3,4} Although this potential role of VZV in the development of GCA has not been substantiated by other investigators, and remains controversial, Gilden suggested adjunctive antivirals be considered in the treatment of GCA.⁵

The incidence rate (IR) of GCA varies widely by country, being the highest in northern Europe and lowest in Asia.^{2,6} We hypothesized that if VZV contributed to GCA, the GCA IRs per 100,000 subjects, 50 years of age or older (IR_{GCA}) per country should correlate with the local herpes zoster IRs (IR_{HZ}). To test this hypothesis, we performed a regression analysis using the published IR_{GCA} and IR_{HZ} from different countries.

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Methods

The IR_{GCA} was searched for on PubMed, Embase, and Google Scholar from inception to July 1, 2017 using the search terms: incidence, epidemiology, country, temporal arteritis and GCA. The same search was repeated using herpes zoster and shingles in place of the arteritis terms.

The country specific IRs for subjects 50 years of age and older were recorded per 100,000 population for GCA, and per 1,000 person-years for HZ. If IRs were provided for multiple years, the results were averaged (Table 1).

The IR_{GCA} in Japan was calculated using Koboyashi's reported prevalence rate of 1.47 per 100,000 in subjects aged 50 years or older, with average age of onset of 71.5 years.⁷ Lifespan is thought not to be affected by GCA unless the patient has aortic aneurysm or dissection.⁸ The average life expectancy in Japan is 83.3 years.⁹ As GCA is a rare disease and recurrent, the IR was estimated as the prevalence rate/duration of disease = 1.3 per million subjects 50 years or older.

Since the peak onset of GCA is in the 8th decade,¹⁰ we also examined the IR of HZ in 70 year-olds. If the age brackets straddled our chosen age cut-offs, the IR values from the two adjacent brackets were averaged.

Only countries/regions that had IRs available for both GCA and HZ were used for analysis. Paired *t*-test was used to examine the time difference in year of publication between the GCA and HZ studies for each country. There was inadequate information in the GCA articles to consistently calculate the within-study standard errors needed for meta-regression. Pearson product-moment correlation coefficients,

and linear regression with and without robust standard errors was performed. White's test was used to test for heteroscedasticity. All statistical tests were conducted with Stata 14.2 (StataCorp LP, College Station, TX, USA), and a two-sided *p* < 0.05 was considered statistically significant.

Results

The IRs for both GCA and HZ were available for 14 countries (Table 1), and plotted on Figure 1. With the exception of Olmsted County and the United Kingdom, the availability of IR_{GCA} and IR_{HZ} from the same time frame and corresponding geographic region was limited. Eight of the 14 countries (57%) in Table 1 were overlapping in the time frame of the corresponding GCA and HZ studies. On paired *t*-test, the GCA studies were published on average 4.5 years before the HZ studies (*p* = 0.09). A published IR_{GCA} for Iceland was available. The IR_{HZ} for Iceland was only available for the 60-year age group only (4.7 per 1,000), but not the 50-year-old or 70-year-old age groups, and as such was not used.

Pearson product-moment correlation coefficient (*r*) comparing IR_{GCA} with: IR_{HZ} in 50 year-olds was -0.51 (*p* = 0.07), and IR_{HZ} in 70-year-olds was -0.40 (*p* = 0.16). Linear regression with robust standard errors showed a regression coefficient (β) -2.92 (95% CI -5.41, -0.43; *p* = 0.025) between the IR_{GCA} \geq 50-year-olds, and the IR_{HZ} in 50-year-olds. For the IR_{HZ} in 70-year-olds, no statistically significant linear dependence of the mean IR_{GCA} on IR_{HZ} was detected (β = -1.78, 95% CI -4.10, 0.53; *p* = 0.12). White's test did not suggest heteroscedasticity (Table 2).

Table 1 Incidence rates of giant cell arteritis and herpes zoster per country

Country	GCA study: year published (study period)/region	IR _{GCA}	HZ study: year/region	IR _{HZ50}	IR _{HZ70}	Time overlap
Norway, B+C ³⁷	2014 (2006–2012)/South	21	2016 (2008–2012)/National ³⁸	2.8	7.0	Yes
Finland, B+C ³⁹	1992 (1984–1988)/West Nyland	26.2	2010 (2000–2006)/Tuusula, Kangasala, Salo ⁴⁰	2.5	6.5	No
Sweden, B ⁴¹	2015 (1997–2010)/Skane	14.1	2013 (2006–2010)/National ⁴²	2.5	8.0	Yes
United Kingdom, B+C ⁴³	2006 (1990–2001)/National	22	2003 (1991–2000)/National ⁴⁴	4.0	9.3	Yes
USA, C ⁴⁵	2015 (2000–2009)/Olmsted Cty	19.8	2016 (1945–2007)/Olmsted City ⁴⁶	4.5	8.4	Yes
Spain, B ⁴⁷	2007 (1981–2005)/Lugo	10.13	2013 (2007–2010)/Valencian Community ⁴⁸	4.8	9.8	No
New Zealand, B ⁴⁹	2011 (1996–2005)/Otago	12.73	2014 (2009–2013)/Lower Hutt ⁵⁰	6.1	7.3	No
Israel, B+C ⁵¹	2007 (1980–2004)/Jerusalem	11.3	2013 (2006–2010)/Tel Aviv ⁵²	5.8	11.8	No
Canada, B ⁵³	2007 (1998–2003)/Saskatoon	9.4	2011 (1992–2010)/Ontario ⁵⁴	3.7	7.4	Yes
France, B+C ⁵⁵	1982 (1970–1979)/Loire-Atlantique	9.4	2010 (2005–2007)/National ⁵⁶	4.2	8.7	No
Italy, B+C ⁵⁷	2017 (1986–2012)/Reggio Emilia	5.8	2010 (2003–2005)/National ⁵⁸	3.6	7.7	Yes
Australia, B ⁵⁹	2013 (1992–2011)/Adelaide	3.2	2008 (1998–2006)/National ⁶⁰	6.5	11.5	Yes
Germany, C ⁶¹	2005 (1998–2002)/Schlewig-Holstein	3.3	2011 (2007–2008)/National ⁶²	6.2	11.3	No
Japan, Cal ⁷	2003 (1998)/National	0.13	2009 (1997–2006)/Miyazaki ⁶³	3.9	7.4	Yes

Notes: B, biopsy proven; C, clinical criteria for diagnosis; Cal, calculated from published prevalence rate; Time overlap, the incidence rates for GCA and HZ were from the same time period.

Abbreviations: GCA, giant cell arteritis; IR, incidence rate; IR_{GCA}, giant cell arteritis incidence rates per 100,000 subjects, 50 years of age or older; HZ, herpes zoster; IR_{HZ50}, herpes zoster incidence rates in 50-year-old subjects per 1,000 person years; IR_{HZ70}, herpes zoster incidence rates in 70-year-old subjects per 1,000 person years.

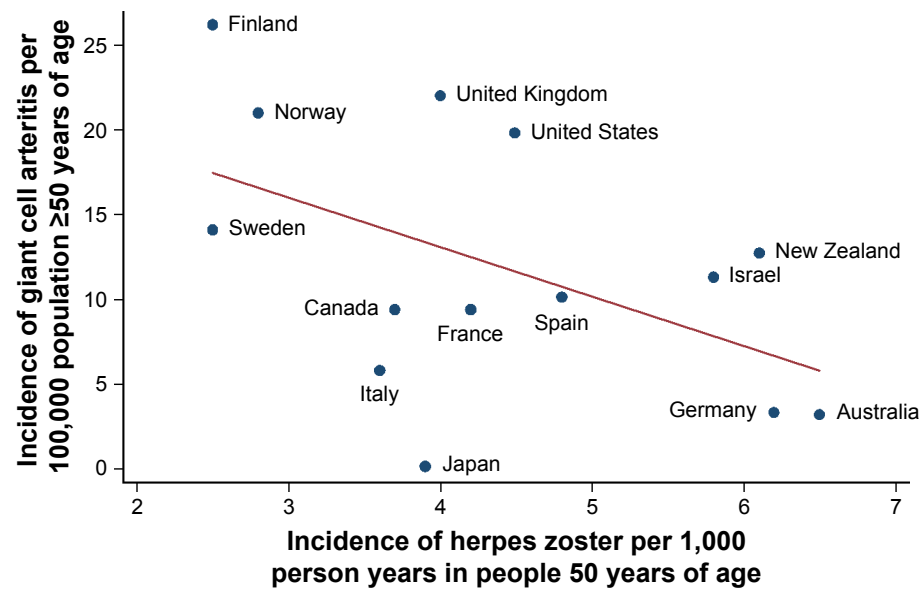


Figure 1 Incidence of giant cell arteritis versus incidence of herpes zoster per country.

Notes: Each dot represents a country's intersecting incidence rates for giant cell arteritis in subjects 50 years or older, and herpes zoster in 50 year-old subjects. The negative sloping red line is the line of best linear fit using the least squares method.

This ecologic study does not support a positive biologic gradient between the IR_{HZ} and IR_{GCA} . Subgroup regression analyses of the per country IR_{GCA} and IR_{HZ} , with and without overlapping timeframes were not statistically significant and did not show a positive regression coefficient.

Discussion

Infections can predispose to systemic vasculitis by mechanisms such as molecular mimicry, epitope spreading, immune response to subdominant epitopes normally hidden from T-cell recognition, or bystander activation.¹¹ If there is a causal relationship between HZ and GCA it is important to define since HZ can be potentially prevented with the shingles vaccine, and because the treatment of GCA might benefit from adjunctive antivirals.

VZV and GCA have some overlapping features. Dendritic cells are thought to play a central role in VZV infection and

the immunopathogenesis of GCA.^{12–14} HZ ophthalmicus or multifocal VZV vasculopathy with temporal artery infection may mimic the presentation of GCA. Varicella zoster vasculopathy and GCA can both cause optic neuropathy, cranial nerve palsy, and stroke.

Temporal artery biopsy studies have shown conflicting results on the association of VZV and GCA. Gilden et al and Nagel et al suggested that VZV triggers the immunopathology of GCA, and found increase of 74% VZV in temporal artery biopsy specimens from patients with GCA.^{3–5,15} However, with the exception of Mitchell and Font,¹⁶ other investigators have not found substantial VZV in the arterial specimens of biopsy-proven GCA or clinically diagnosed GCA.^{17–22} False positive immunohistochemistry from antibody cross-reactivity to shared epitopes between VZV proteins and arterial smooth muscle elements suggest caution when interpreting pathology findings.²³ Gilden and Nagel acknowledge

Table 2 Correlation and linear regression of the incidence rates of giant cell arteritis versus herpes zoster

Zoster incidence rate age groups	Number of countries	Correlation coefficient	Regression coefficient	p-value, R ²	p-value with robust SE	p-value for white's test
50-year-olds, all countries	14	−0.51	−2.92	p=0.07, R ² =0.26	p=0.025	p=0.28
70-year-olds, all countries	14	−0.40	−1.78	p=0.16, R ² =0.16	p=0.12	p=0.42
50-year-olds, time overlap	8	−0.38	−2.66	p=0.35, R ² =0.14	p=0.06	p=0.12
70-year-olds, time overlap	8	−0.15	−0.88	p=0.72, R ² =0.02	p=0.69	p=0.88
50-year-olds, no overlap	6	−0.80	−4.24	p=0.06, R ² =0.63	p=0.05	p=0.93
70-year-olds, no overlap	6	−0.74	−2.63	p=0.09, R ² =0.54	p=0.14	p=0.09

Notes: Correlation coefficient, Pearson product-moment correlation coefficient (*r*); regression coefficient, linear regression coefficient; time overlap, the incidence rates for GCA and HZ were from the same time period; no overlap, the incidence rates for GCA and HZ were from different time periods.

Abbreviations: GCA, giant cell arteritis; HZ, herpes zoster; SE, standard error.

that “the presence of VZV in about 20% of temporal artery biopsies from non-GCA post-mortem controls also suggests that VZV alone is not sufficient to produce disease”.⁵

A population-based cohort study did not find an increased risk of HZ in patients with GCA compared to non-GCA subjects, even during the first 6 months after glucocorticoid initiation, when patients are on the highest doses.²⁴ A large nested case control study determined that HZ had a modest incidence rate ratio of 1.17 in association with incident GCA.²⁵ A review of two large administrative databases found a two-fold increased risk of GCA with complicated HZ.²⁶

Our ecologic study did not show a positive biologic gradient between the IR_{HZ} and IR_{GCA} . Limitations of this study include possible ecologic fallacy, time, location and/or selection biases, the limited availability of IR_{GCA} and IR_{HZ} , and variable trends in IR. By and large the IR_{HZ} are increasing.²⁷ Zoster sine herpete and asymptomatic VZV infection may have affected our analysis. The IR_{GCA} may be increasing,² decreasing,⁶ or cyclical.²⁸ Furthermore, the IR_{GCA} are higher when cases of clinically diagnosed GCA are included with biopsy-proven GCA. It is unlikely that the IR_{HZ} in Table 1 were significantly affected by zoster vaccination. The Oka/Merck zoster vaccine decreases the risk of shingles by only 51%,²⁹ and was approved for use in the United States and European Union in 2006,^{30,31} and in Canada in 2008.³² The Olmsted county HZ study published in 2016 reviewed two sets of patients, the latest of which were from 1980 to 2007. In the United States a 5% random sample of Medicare seniors were first offered zoster vaccine in 2007, and uptake was low at 3.9%.³³ The first two European countries to recommend nation-wide zoster vaccination for seniors 65 to 74 years of age were the United Kingdom and France in 2013.³⁴ The Australian and Ontario, Canada immunization programs for seniors began in 2016.^{35,36}

Conclusion

The discordant IRs for HZ and GCA question the biologic plausibility of clinically overt HZ as the sole immunopathogenic trigger for GCA. Geo-epidemiology may help elucidate the relationship between VZV and GCA, but more widely available, accurate and updated IRs from different countries are required.

Disclosure

The authors report no conflicts of interest in this work.

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